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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,994	02/15/2002	Usha Kasid	219604	9186

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,994	KASID ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3-4-04, 2-17-04, 9*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 2-15-02.

Claims 1-22 are pending in the instant application.

Objection to the Specification

It is unclear on page 43, line 16, what is meant by "Anti Chemotherapeutic." This section of the specification describes treatment of prostate cancer using the antisense of SEQ ID NO: 1 in combination with the chemotherapeutic agent, mitoxantrone.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 9, line 3, it is unclear what is meant by "phosphorothiotated" (e.g. replacing "phosphorothiotated" with –phosphorothioated—would be remedial).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 12-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods for chemosensitizing tumor tissue comprising the administration of at least one lipid encapsulated oligonucleotide and optionally a chemotherapeutic agent, which agent is optionally an antimetabolite, a natural product, a hormone, an antagonist, a substituted urea, a methylhydrazine derivative, a small molecule inhibitor, peptide, or an antibody. The specification and claims do not indicate or describe the elements which are essential to the genera comprising an oligonucleotide, an anti-metabolite, a natural product, a hormone, an antagonist, a substituted urea, a methylhydrazine derivative, a small molecule inhibitor, peptide, or an antibody. The specification and claims do not indicate what distinguishing attributes are concisely shared by the members of these broad genera, and the disclosure does not clarify what the common attributes are that are encompassed by these genera. The scope of the claims includes a myriad of structural variants (e.g. any oligonucleotide sequence, any hormone, any anti-metabolite, any natural product, any antagonist to anything or any process, any derivative to methylhydrazine, any substitution to urea, a peptide of any sequence or size, a small molecule inhibitor of anything and any antibody), and the genera are highly variant because a significant number of structural differences between members

of a given genus is permitted. Concise structural features that could distinguish structures or compounds within each genus from others are missing from the disclosure. The specification fails to teach or adequately describe a representative number of species in each genus (e.g. an antisense oligonucleotide of SEQ ID NO: 1 and the chemotherapeutic agent metoxantrone are taught in the instant specification) such that common attributes or characteristics concisely identifying members of each proposed genus are exemplified. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the various genera claimed. Thus, Applicant was not in possession of the claimed genera.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 12-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enhanced delivery of any oligonucleotide to target cells in vitro comprising the administration of an oligonucleotide (of 40 nucleobases or less) encapsulated in cationic liposomes consisting of the cationic lipid, phosphatidylcholine and cholesterol and for the chemosensitization of tumor tissue in vivo comprising the administration of SEQ ID NO: 1 and metoxantrone, does not reasonably provide enablement for the

chemosensitization of tumor tissue comprising the administration of any oligonucleotide and optionally further comprising the administration of any chemotherapeutic agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of chemosensitizing tumor tissue comprising the administration of a composition comprising at least one oligonucleotide encapsulated in cationic liposomes consisting of a cationic lipid, phosphatidylcholine and cholesterol, and optionally further comprising a chemotherapeutic agent. The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found

more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Likewise, Peracchi cautions investigators about the problems of achieving in vivo efficacy using oligonucleotide based approaches: "Much progress has been made towards understanding the structure and mechanism of these catalysts [ribozymes]...Despite this, it is not yet clear whether these molecules can be developed into clinically useful pharmaceutical preparations." (See the abstract on page 47). Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (See text on page 51).

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials

in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of chemosensitizing tumor tissue comprising the administration of a composition comprising at least one oligonucleotide of any sequence and encapsulated in cationic liposomes consisting of a cationic lipid, phosphatidylcholine and cholesterol, and optionally further comprising the administration of any chemotherapeutic agent. The

specification teaches the enhanced delivery of the oligonucleotide of SEQ ID NO: 1 (of 20 nucleobases) to tumor cells in vitro, which oligonucleotide is encapsulated in cationic liposomes consisting of DMTAP, phosphatidylcholine and cholesterol. The specification also teaches the chemosensitization of pancreatic and prostate tumors in vivo comprising the systemic administration of a compositions comprising the anti-Raf antisense oligonucleotide of SEQ ID NO: 1 encapsulated in cationic liposomes consisting of DMTAP, phosphatidylcholine and cholesterol, and further comprising the chemotherapeutic agent metoxantrone. One skilled in the art would not accept on its face the examples given in the specification of the in vitro enhanced delivery of oligonucleotides to tumor target cells following administration of the encapsulated oligonucleotide of SEQ ID NO: 1, or the in vivo chemosensitization of tumors following administration of SEQ ID NO: 1 and metoxantrone, as being correlative or representative of the successful chemosensitization of tumors in an organism comprising the administration of any oligonucleotide (an of any size), optionally in combination with any chemotherapeutic agent in view of the lack of guidance in the specification and known unpredictability associated with chemosensitization of tumors in an organism using any cationic liposome encapsulating oligonucleotide..

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to methods of chemosensitizing any tumor tissue comprising the administration of a composition comprising at least one oligonucleotide of any sequence

encapsulated in cationic liposomes consisting of a cationic lipid, phosphatidylcholine and cholesterol, and optionally further comprising a chemotherapeutic agent. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, appropriate target genes whose inhibition of expression leads to chemosensitization of tumors, and corresponding antisense that inhibit appropriate target gene expression in vivo, modes of delivery and formulations to target appropriate cells and /or tissues harboring the corresponding target genes whereby target gene expression is inhibited in cells in vivo and chemosensitization is provided for any tumor. Since the specification fails to provide any particular guidance for targeting the appropriate genes in appropriate target tumor cells with antisense, whereby the expression of appropriate genes is inhibited by antisense administered, and whereby chemosensitization of tumors is provided, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10 and 11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 6 and 13 of U.S. Patent No. 6,126,965. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 10 and 11 of the instant application and claims 1, 6 and 13 are drawn to compositions comprising the oligonucleotide of SEQ ID NO: 1 encapsulated in cationic liposomes comprising either DDAB or DMTAP as the cationic lipid, and further comprising phosphatidylcholine and cholesterol, which oligonucleotide comprises the stabilizing modification of phosphorothioate internucleotide linkages at each end of the oligonucleotide (see also col. 2 of USPN 6,126,965, lines 55-59).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

7-7-04

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